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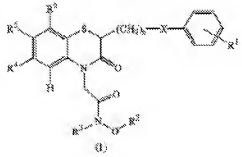
(71)Applicant : **SUMITOMO PHARMACEUT CO LTD**
(72)Inventor : **MITSUMIZO FUMIO**
**KAMIKAWA YUMIKO**
**HOI HITOSHI**
**HORIUCHI YOSHIHIRO**

## (54) BENZOTHIAZIN-3-ONE DERIVATIVE

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a medicine useful for treating and preventing articular diseases such as osteoarthritis and chronic rheumarthritis, cancer cell metastasis, gingivitis and the like.
SOLUTION: This benzothiadin-3-one derivative is represented by formula (1) [X is a single bond or a heterogeneous atom; (n) is an integer of 1 to 6; R1 is H, a halogen atom or a substituent; R2 is H or a substituent; R3 is H or a substituent (R2 and R3 are simultaneously not H) or R2 and R3 are bound to form a heterogeneous ring; R4, R5 and R6 are each a substituent] or its salt.



## EFFECT OF THE INVENTION

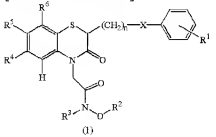
[Effect of the Invention]A new benzothiazine 3-one derivative can be provided by this invention. Since it is metabolized in in the living body and matrix-metallo-protease inhibiting activity is shown while this invention compound shows good oral absorbency, this invention compound is useful as the treating agent of articular diseases, such as osteoarthritis and rheumatoid arthritis, the metastasis control agent of a cancer cell, or an anti-inflammatory agent.

## TECHNICAL PROBLEM

[Problem to be solved by the invention]The problem of this invention is in offer of drugs useful as treating agents, such as metastasis of articular diseases, such as osteoarthritis and rheumatoid arthritis, and a cancer cell, and gingivitis, and preventive.
[0006]

## MEANS

[Means for solving problem]In order that this invention persons may solve an aforementioned problem, as a result of repeating examination wholeheartedly, while a benzothiazine 3-one derivative shows good oral absorbency, It is metabolized in in the living body, finds out that it is a new prodrug which reveals matrix-metallo-protease inhibiting activity, and came to complete this invention.
[0007]That is, the invention in this application is a formula (1) of (1) following.
[Chemical formula 2]



(1)

(X express a single bond, a sulfur atom, or an oxygen atom among a formula, and n) Express the integer of 1-6 and $R^1$ A hydrogen atom, a halogen atom, The alkyl group which may be replaced, the alkoxy group which may be replaced, an alkyl sulfonyl group, Express the aryloxy group or the heteroaryloxy group which may be replaced which may be replaced, and $R^2$, A hydrogen atom, the alkyloxy carbonyl which may be replaced, the alkyl which may be replaced, Express the carbamoyl group which may be replaced, or the annular carbamoyl group which may be replaced, or $R^3$, Or [ it expresses a hydrogen atom, the alkyloxy carbonyl which may be replaced, or the alkyl which may be replaced (however, $R^2$ and $R^3$) ], it does not become a hydrogen atom simultaneously. Or $R^2$ and $R^3$ join together, express heterocycle and $R^4$, A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl group, a substituted alkyl group, Express an alkyl sulfonyl group, the carbamoyl group which may be replaced, or the alkyloxy carbonyl group which may be replaced, and $R^5$ A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl group, a substituted alkyl group, Express an alkyl sulfonyl group, the carbamoyl group which may be replaced, the annular carbamoyl group which may be replaced, or the alkyloxy carbonyl group which may be replaced, and $R^6$, A hydrogen atom, a carboxy group, or the alkyloxy carbonyl group that may be replaced is expressed. The benzothiazine 3-one derivative expressed or its salt.
(2) The benzothiazine 3-one derivative or its salt of the above-mentioned (1) description whose n is an integer of 1 to 4.
(3) A benzothiazine 3-one derivative or its salt the above (1) whose $R^1$ is a halogen atom, an alkoxy group which may be replaced, an alkyl sulfonyl group, an aryloxy group which may be replaced, or a heteroaryloxy group which may be replaced, or given in (2).
(4) The benzothiazine 3-one derivative or its salt of the above-mentioned (3) description whose X is a single

bond.
(5) The benzothiazine 3-one derivative or its salt of the above-mentioned (4) description whose n is 1.
$R^4$ (6) A carboxy group, a tetrazole group, an imidazole group, A benzothiazine 3-one derivative or its salt given in either of above-mentioned (1) - (5) which is a substituted alkyl group, an alkyl sulfonyl group, a carbamoyl group that may be replaced, or an alkyloxy carbonyl group which may be replaced.
$R^5$ (7) A carboxy group, a tetrazole group, an imidazole group, A benzothiazine 3-one derivative or its salt given in either of above-mentioned (1) - (5) which is a substituted alkyl group, an alkyl sulfonyl group, a carbamoyl group that may be replaced, an annular carbamoyl group which may be replaced, or an alkyloxy carbonyl group which may be replaced.
(8) A benzothiazine 3-one derivative or its salt given in either of above-mentioned (1) - (7) whose $R^1$ is trifluoro methoxy groups.
(9) A benzothiazine 3-one derivative or its salt given in either of above-mentioned (1) - (7) which is an aryloxy group by which $R^1$ may be replaced.
[0008](10) The above (1) Medicinal composition which contains the benzothiazine 3-one derivative of a description, or its salt in either of - (9).
(11) The above (1) Matrix-metallo-protease inhibitor which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(12) The above (1) Articular disease treating agent which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(13) The above (1) Cancer metastasis inhibitor which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(14) The above (1) Anti-medical-treatment-for-inflammation agent which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(15) The above (1) Periodontitis treating agent which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(16) The above (1) Medicinal composition for taking orally which contains the benzothiazine 3-one derivative of a description, or its salt in either of - (9). It is related with **.
[0009]
[Embodiment of the Invention]The substituent in this invention compound is explained below concretely. As an alkyl group in $R^1$, it is mentioned by the straight chain or branching alkyl group of the carbon numbers 1-6, and specifically, For example, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, etc. are mentioned. As a substituent in the substituted alkyl group of $R^1$, For example, a hydroxyl group, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) for example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1,1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned. etc. -- it may be mentioned, an adjoining alkoxy group may join together, for example, a methylenedioxy group and an ethylene dioxy group may be formed. .As the number of the substituents in the substituted alkyl group of $R^1$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred. As an alkoxy group in $R^1$, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, for example, and, specifically, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned, for example. As a substituent in the substitution alkoxy group of $R^1$, For example, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) for example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned. etc. -- it is mentioned. As an alkyl sulfonyl group in $R^1$, For example, the alkyl sulfonyl group of the carbon numbers 1-6 is mentioned, and methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc. are specifically mentioned.
[0010]As an aryloxy group in $R^1$, the aryloxy group of the carbon numbers 6-10 is mentioned, and, specifically, a phenyloxy group etc. are mentioned, for example. As a substituent in the substitution aryloxy group of $R^1$, For example, a hydroxyl group, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) For example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, The alkoxy group (for example, trifluoromethoxy, 1,1,1-trifluoroethoxy, pentafluoro ethoxy ** trichloromethoxy, etc. are mentioned.) replaced with halogen atoms, such as 1,1-

dimethylethoxy, pentoxy, and HEKISOKISHI, is mentioned. an adjoining alkoxy group may join together, for example, a methylenedioxy group and an ethylene dioxy group may be formed -- an alkyl sulfonyl group (for example, the alkyl sulfonyl group of the carbon numbers 1-6 is mentioned, and specifically.) methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc. are mentioned. etc. -- it is mentioned. As the number of the substituents in the substitution aryloxy group of $R^1$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred. As a heteroaryloxy group in $R^1$, the heteroaryloxy group which has 1 to 2 is mentioned in a nitrogen atom, and, specifically, a pyridyloxy group, a pyrimidyl oxy group, etc. are mentioned, for example. As a substituent in the substitution heteroaryloxy group of $R^1$, For example, a hydroxyl group, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) For example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1,1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned. The alkoxy group (for example, trifluoromethoxy, 1,1,1-trifluoroethoxy, pentafluoro ethoxy ** trichloromethoxy, etc. are mentioned.) etc. which were replaced with the halogen atom are mentioned. As the number of the substituents in the substitution heteroaryloxy group of $R^1$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred.

## DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application]This invention relates to a new benzothiazine 3-one derivative or its salt. It is related with the new new benzothiazine 3-one derivative which checks matrix-metallo-protease activity in in the living body in detail. More particularly, it is metabolized in in the living body, and is related with the prodrug which checks matrix-metallo-protease activity.

[0002]

[Description of the Prior Art]a group to which collagen and the extra-cellular matrix represented by the proteoglycan which constitute connective tissue are called matrix protease -- it is metabolized with a proteolytic enzyme. The matrix metallo protease Collagenase (the matrix metallo protease 1, MMP-1), The gelatinase A (the matrix metallo protease 2, MMP-2). Stromelysin (the matrix metallo protease 3, MMP-3), 19 kinds are known now [, such as the gelatinase B (the matrix metallo protease 9, MMP-9), the collagenase 3 (the matrix metallo protease 13, MMP-13), and the film knot-pattern matrix metallo protease 1 (MT1-MMP and MMP-14) ]. If an extra-cellular matrix is normal, they are composition of these matrix metallo protease, and a level of secretion, Or it is strictly controlled by the endogenous inhibition substance (for example, TIMP (Tissue Inhibitor of matrix metallo protease)) in the outside of a cell. There are many reports about the relation of the disease which makes condition protease activity rise produced when this balance collapses, and destruction of connective tissue.

[0003]For example, destruction of an articular cartilage in the joint of the osteoarthritis and rheumatoid arthritis patient who are the features. Matrix metallo protease, especially stromelysin, Collagenase is detected with a high level (Arthr.). Rheum., 33, and 388-397(1990); . S.M. Krane etc. and "Modulation. of matrix synthesis and degradation in joint inflammation, The Control of Tissue Damage", A.B.Glauert (Editor), Elsevier Sci.Publ., Amsterdam, 1988, and Ch.14, pp. 179-195; Clin.Chim.Acta, 185, 73-80 (1989); Arthr.Rheum., 27,305-312 (1984); J.Clin.Invest., 84, 678-685 (1989). In order for a cancer cell to permeate and metastasize an organization and to form a secondary tumor, Since the step which decomposes basement membrane is indispensable, the manifestation of matrix metallo protease, such as the gelatinases A and B, and enzyme activity, Permeation of a cancer cell, related (FEBS J. and 5.) to transition ability 2145-2154 (1991); Trends. Genet., 6, 121-125 (1990); Cancer Res., 46, 1-7 (1986); Cell, 64, 327-336(1990);Cancer and Metastasis Rev., 9,305-319 (1990). It is checked in the fibrocyte taken out from the organization which has shown the symptoms of gingivitis that collagenase and stromelysin are activated (J. Periodontal Res., 16, 417-424 (1981)). Those enzyme levels are related with the seriousness of gingivitis (J. Periodontal Res., 22, 81-88 (1987)).

[0004]The collagenase 3 (the matrix metallo protease 13, MMP-13) A chronic articular rheumatism patient's synovial membrane, The osteoarthritis. revealed (J. -- Clin.Invest., 97, 2011-2019(1996); J.Rheumatol., 23, 509-595(1996); J.Biol.Chem., and 271.) by the Homo sapiens chondrocyte whose symptoms are shown 23577-23581 (1996); J.Clin.Invest., 97, 761-768 (1996). MMP-13 has the powerful decomposition activity over the II type collagen and the ugli can which are the main extra-cellular-matrix constituents of a cartilage matrix,

Relation with the cartilage osteoarthritis and articular rheumatism is pointed out (J. Biol.Chem., 271, 1544-1550(1996); FEBS Lett., 380, 17-20 (1996)). Therefore, matrix-metallo-protease inhibitor can be used as treating agents, such as metastasis of articular diseases, such as osteoarthritis and rheumatoid arthritis, and a cancer cell, and gingivitis, and preventive. Matrix metallo protease besides destruction of the above extra-cellular matrices, The conversion from the latent type of a tumor necrosis factor to a matured type (Nature, 370, 555-557 (1994)), Decomposition of the alpha 1-antitrypsin which is serine protease inhibitor (FEBS Lett., 279, 191-194 (1991)), It is participating in the activation (Biochemistry, 29, 10261-10670(1990); J.Biol.Chem., 267, 21712-21719 (1992)) by both matrix metallo protease. Therefore, matrix-metallo-protease inhibitor can be used as an anti-inflammatory agent. However, the matrix-metallo-protease inhibitor in which activity sufficient as drugs till the present is shown is not known.

[0005]

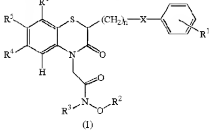
[Problem to be solved by the invention]The problem of this invention is in offer of drugs useful as treating agents, such as metastasis of articular diseases, such as osteoarthritis and rheumatoid arthritis, and a cancer cell, and gingivitis, and preventive.

[0006]

[Means for solving problem]In order that this invention persons may solve an aforementioned problem, as a result of repeating examination wholeheartedly, while a benzothiazine 3-one derivative shows good oral absorbency, It is metabolized in in the living body, finds out that it is a new prodrug which reveals matrix-metallo-protease inhibiting activity, and came to complete this invention.

[0007]That is, the invention in this application is a formula (1) of (1) following.

[Chemical formula 2]



(1)

(X express a single bond, a sulfur atom, or an oxygen atom among a formula, and n) Express the integer of 1-6 and $R^1$ A hydrogen atom, a halogen atom, The alkyl group which may be replaced, the alkoxy group which may be replaced, an alkyl sulfonyl group, Express the aryloxy group or the heteroaryloxy group which may be replaced which may be replaced, and $R^2$, A hydrogen atom, the alkyloxy carbonyl which may be replaced, the alkyl which may be replaced, Express the carbamoyl group which may be replaced, or the annular carbamoyl group which may be replaced, or $R^3$, Or [ it expresses a hydrogen atom, the alkyloxy carbonyl which may be replaced, or the alkyl which may be replaced (however, $R^2$ and $R^3$) ], it does not become a hydrogen atom simultaneously. Or $R^2$ and $R^3$ join together, express heterocycle and $R^4$, A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl group, a substituted alkyl group, Express an alkyl sulfonyl group, the carbamoyl group which may be replaced, or the alkyloxy carbonyl group which may be replaced, and $R^5$ A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl group, a substituted alkyl group, Express an alkyl sulfonyl group, the carbamoyl group which may be replaced, the annular carbamoyl group which may be replaced, or the alkyloxy carbonyl group which may be replaced, and $R^6$, A hydrogen atom, a carboxy group, or the alkyloxy carbonyl group that may be replaced is expressed. The benzothiazine 3-one derivative expressed or its salt.

(2) The benzothiazine 3-one derivative or its salt of the above-mentioned (1) description whose n is an integer of 1 to 4.

(3) A benzothiazine 3-one derivative or its salt the above (1) whose $R^1$ is a halogen atom, an alkoxy group which may be replaced, an alkyl sulfonyl group, an aryloxy group which may be replaced, or a heteroaryloxy group which may be replaced, or given in (2).

(4) The benzothiazine 3-one derivative or its salt of the above-mentioned (3) description whose X is a single bond.

(5) The benzothiazine 3-one derivative or its salt of the above-mentioned (4) description whose n is 1.

$R^4$ (6) A carboxy group, a tetrazole group, an imidazole group, A benzothiazine 3-one derivative or its salt given in either of above-mentioned (1) - (5) which is a substituted alkyl group, an alkyl sulfonyl group, a carbamoyl group that may be replaced, or an alkyloxy carbonyl group which may be replaced.

$R^5$ (7) A carboxy group, a tetrazole group, an imidazole group, A benzothiazine 3-one derivative or its salt

given in either of above-mentioned (1) - (5) which is a substituted alkyl group, an alkyl sulfonyl group, a carbamoyl group that may be replaced, an annular carbamoyl group which may be replaced, or an alkyloxy carbonyl group which may be replaced.
(8) A benzothiazine 3-one derivative or its salt given in either of above-mentioned (1) - (7) whose $R^1$ is trifluoro methoxy groups.
(9) A benzothiazine 3-one derivative or its salt given in either of above-mentioned (1) - (7) which is an aryloxy group by which $R^1$ may be replaced.
[0008](10) The above (1) Medicinal composition which contains the benzothiazine 3-one derivative of a description, or its salt in either of - (9).
(11) The above (1) Matrix-metallo-protease inhibitor which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(12) The above (1) Articular disease treating agent which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(13) The above (1) Cancer metastasis inhibitor which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(14) The above (1) Anti-medical-treatment-for-inflammation agent which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(15) The above (1) Periodontitis treating agent which makes the benzothiazine 3-one derivative of a description, or its salt either of - (9) with an active principle.
(16) The above (1) Medicinal composition for taking orally which contains the benzothiazine 3-one derivative of a description, or its salt in either of - (9). It is related with **.
[0009]
[Embodiment of the Invention]The substituent in this invention compound is explained below concretely. As an alkyl group in $R^1$, it is mentioned by the straight chain or branching alkyl group of the carbon numbers 1-6, and specifically, For example, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, etc. are mentioned. As a substituent in the substituted alkyl group of $R^1$, For example, a hydroxyl group, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) for example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1,1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned. etc. -- it may be mentioned, an adjoining alkoxy group may join together, for example, a methylenedioxy group and an ethylene dioxy group may be formed. .As the number of the substituents in the substituted alkyl group of $R^1$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred. As an alkoxy group in $R^1$, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, for example, and, specifically, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned, for example. As a substituent in the substitution alkoxy group of $R^1$, For example, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) for example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1, and 1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned. etc. -- it is mentioned. As an alkyl sulfonyl group in $R^1$, For example, the alkyl sulfonyl group of the carbon numbers 1-6 is mentioned, and methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc. are specifically mentioned.
[0010]As an aryloxy group in $R^1$, the aryloxy group of the carbon numbers 6-10 is mentioned, and, specifically, a phenyloxy group etc. are mentioned, for example. As a substituent in the substitution aryloxy group of $R^1$, For example, a hydroxyl group, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) For example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, The alkoxy group (for example, trifluoromethoxy, 1,1,1-trifluoroethoxy, pentafluoro ethoxy ** trichloromethoxy, etc. are mentioned.) replaced with halogen atoms, such as 1,1-dimethylethoxy, pentoxy, and HEKISOKISHI, is mentioned. an adjoining alkoxy group may join together, for example, a methylenedioxy group and an ethylene dioxy group may be formed -- an alkyl sulfonyl group (for example, the alkyl sulfonyl group of the carbon numbers 1-6 is mentioned, and specifically.) methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc. are mentioned. etc. -- it is mentioned. As the number of the substituents in the substitution aryloxy group of $R^1$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or

different ] is preferred. As a heteroaryloxy group in $R^1$, the heteroaryloxy group which has 1 to 2 is mentioned in a nitrogen atom, and, specifically, a pyridyloxy group, a pyrimidyl oxy group, etc. are mentioned, for example. As a substituent in the substitution heteroaryloxy group of $R^1$, For example, a hydroxyl group, a halogen atom (for example, fluoride, chlorine, bromine, iodine, etc. are mentioned.), The alkoxy group of the carbon numbers 1-6 (for example, the straight chain or branching alkoxy group of the carbon numbers 1-6 is mentioned, and, specifically) For example, methoxy and ethoxy ** propoxy, 2-propoxy, butoxy, 1,1-dimethylethoxy, pentoxy, HEKISOKISHI, etc. are mentioned. The alkoxy group (for example, trifluoromethoxy, 1,1,1-trifluoroethoxy, pentafluoro ethoxy ** trichloromethoxy, etc. are mentioned.) etc. which were replaced with the halogen atom are mentioned. As the number of the substituents in the substitution heteroaryloxy group of $R^1$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred.

[0011]As an alkyloxy carbonyl group in $R^2$, For example, it is mentioned by the alkyloxy carbonyl group of the carbon numbers 2-7, and specifically, For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As an alkyl group in the substituted alkyl of $R^2$, The straight chain or branching alkyl group of the carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, etc. are mentioned, for example. As a substituent in the substituted alkyl group of $R^2$, Alkyloxy carbonyl group (for example, the alkyloxy carbonyl group of the carbon numbers 2-7 is mentioned, and, specifically) For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. further -- a maleic anhydride, a methylmaleic anhydride, etc. -- etc. -- it is mentioned. As a carbamoyl group by which $R^2$ may be replaced, Alkyl carbamoyl group (for example, the alkyl carbamoyl group of the carbon numbers 1-6) [ mention and ] Specifically Methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, 2-propylcarbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1,1-dimethylethyl carbamoyl, pentylcarbamoyl, hexylcarbamoyl, etc. are mentioned -- a dialkyl carbamoyl group (for example, as a dialkyl carbamoyl group of the carbon numbers 2-12) For example, dimethylcarbamoyl, diethylcarbamoyl, ethyl methylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl, etc. are mentioned. It is mentioned.

[0012]As an annular carbamoyl group by which $R^2$ may be replaced, A cycloalkyl carbamoyl group (for example, the cycloalkyl carbamoyl group of the carbon numbers 3-7 is mentioned, for example, cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, etc. are mentioned.) is mentioned. As a substituent of the substituted alkyl carbamoyl group in $R^2$, a hydroxyl group, a carboxy group, a halogen atom (for example, a fluorine atom, a chlorine atom, a bromine atom, and iodine atoms are mentioned.), etc. are mentioned. As a substituent of a substitution dialkyl carbamoyl group, a hydroxyl group, a carboxy group, and a halogen atom (for example, a fluorine atom and a chlorine atom.) a bromine atom and iodine atoms are mentioned -- heterocycle (for example, 0 to 1 or oxygen atom **** heterocycle is mentioned in 1 to 2, and an oxygen atom, and, specifically, a nitrogen atom) for example, pyrrolidine, pyrrolidone, piperidine, imidazole, morpholine, and franc ** is mentioned. etc. -- it is mentioned. As a substituent of the substitution cycloalkyl carbamoyl group in $R^2$, a hydroxyl group, a carboxy group, a halogen atom (for example, a fluorine atom, a chlorine atom, a bromine atom, and iodine atoms are mentioned.), etc. are mentioned. As the number of the substituents in the substitution carbamoyl group of $R^2$, a substituted alkyl carbamoyl group, and a substitution cycloalkyl carbamoyl group, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred.

[0013]As an alkyloxy carbonyl group in $R^3$, For example, it is mentioned by the alkyloxy carbonyl group of the carbon numbers 2-7, and specifically, For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As an alkyl group in the substituted alkyl of $R^3$, The straight chain or branching alkyl group of the carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, etc. are mentioned, for example. As a substituent in the substituted alkyl group of $R^3$, Alkyloxy carbonyl group (for example, the alkyloxy carbonyl group of the carbon numbers 2-7 is mentioned, and, specifically) For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. A maleic anhydride, a methylmaleic anhydride, etc. are mentioned further. However, $R^2$ and $R^3$ do not serve as a hydrogen atom simultaneously. As heterocycle which $R^2$ and $R^3$ combine and form, isooxazolidine 3,5-dione, 4,4-dimethyliso oxazolidine 3,5-dione, etc. are mentioned, for example.

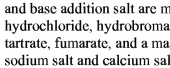
[0014]As an alkyl group of the substituted alkyl group in $R^4$, The straight chain or branching alkyl group of the

carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, etc. are mentioned, for example. As a substituent in the substituted alkyl group of $R^4$, a hydroxyl group, an amino group, a guanidino group, a carboxy group, a halogen atom, etc. are mentioned. As the number of the substituents in the substituted alkyl group of $R^4$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred. As an alkyl sulfonyl group in $R^4$, For example, the alkyl sulfonyl group of the carbon numbers 1-6 is mentioned, and methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc. are specifically mentioned. As a substitution carbamoyl group in $R^4$, Alkyl carbamoyl group (for example, the alkyl carbamoyl group of the carbon numbers 1-6) [ mention and ] Specifically Methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, 2-propylcarbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1,1-dimethylethyl carbamoyl, pentylcarbamoyl, hexylcarbamoyl, etc. are mentioned -- a cycloalkyl carbamoyl group (for example, the cycloalkyl carbamoyl group of the carbon numbers 3-7 is mentioned, for example.) Cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl etc. are mentioned -- a substituted alkyl carbamoyl group (as an alkyl carbamoyl group portion) The alkyl carbamoyl group of the carbon numbers 1-6 is mentioned, and specifically For example, methylcarbamoyl, Ethylcarbamoyl, propylcarbamoyl, 2-propylcarbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1,1-dimethylethyl carbamoyl, pentylcarbamoyl, Hexylcarbamoyl etc. are mentioned. as a substituent -- a hydroxyl group, a carboxy group, and a halogen atom (for example, a fluorine atom.) a chlorine atom, a bromine atom, and iodine atoms are mentioned -- heterocycle (for example, 0 to 1 or oxygen atom **** heterocycle is mentioned in 1 to 2, and an oxygen atom, and, specifically, a nitrogen atom) for example, pyrrolidine, pyrrolidone, piperidine, imidazole, morpholine, and franc ** is mentioned. etc. -- it is mentioned.

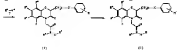
[0015]As the number of the substituents in the substitution carbamoyl group of $R^4$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred. As an alkyloxy carbonyl group in $R^4$, For example, it is mentioned by the alkyloxy carbonyl group of the carbon numbers 2-7, and specifically, For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As a substituent in the substitution alkyloxy carbonyl group of $R^4$, Cycloalkyloxy carbonyloxy group (for example, cycloalkyloxy carbonyloxy group of the carbon numbers 4-8 is mentioned, and, specifically) for example, cyclopropyloxy carbonyloxy, cyclobutyloxy carbonyloxy, cyclopenthyloxycarbonyloxy, cyclohexyloxy carbonyloxy, etc. are mentioned. etc. -- it is mentioned.

[0016]As an alkyl group of the substituted alkyl group in $R^5$, The straight chain or branching alkyl group of the carbon numbers 1-6 is mentioned, and, specifically, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 3-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, etc. are mentioned, for example. As a substituent in the substituted alkyl group of $R^5$, a hydroxyl group, an amino group, a guanidino group, a carboxy group, a halogen atom, etc. are mentioned. As the number of the substituents in the substituted alkyl group of $R^5$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred. As an alkyl sulfonyl group in $R^5$, For example, the alkyl sulfonyl group of the carbon numbers 1-6 is mentioned, and methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc. are specifically mentioned. As a substitution carbamoyl group in $R^5$, Alkyl carbamoyl group (for example, the alkyl carbamoyl group of the carbon numbers 1-6) [ mention and ] Specifically Methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, 2-propylcarbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1,1-dimethylethyl carbamoyl, pentylcarbamoyl, hexylcarbamoyl, etc. are mentioned -- a dialkyl carbamoyl group (for example, as a dialkyl carbamoyl group of the carbon numbers 2-12) For example, dimethylcarbamoyl, diethylcarbamoyl, ethyl methylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl, etc. are mentioned -- a cycloalkyl carbamoyl group (for example, the cycloalkyl carbamoyl group of the carbon numbers 3-7 is mentioned, for example.) Cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl etc. are mentioned -- a substituted alkyl carbamoyl group (as an alkyl carbamoyl group portion, the alkyl carbamoyl group of the carbon numbers 1-6, for example) [ mention and ] Specifically Methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, 2-propylcarbamoyl, butylcarbamoyl, 2-butylcarbamoyl, 3-methylpropyl carbamoyl, 1,1-dimethylethyl carbamoyl, pentylcarbamoyl, hexylcarbamoyl, etc. are mentioned. As a substituent, a hydroxyl group, a carboxy group, a halogen atom. (For example, a fluorine atom, a chlorine atom, a bromine atom, and iodine atoms are mentioned), a substitution dialkyl carbamoyl group (as a dialkyl carbamoyl group portion) For example, as a dialkyl carbamoyl group of the carbon numbers 2-12, dimethylcarbamoyl, diethylcarbamoyl, ethyl methylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl, etc. are mentioned, for example. as a substituent -- a

hydroxyl group, a carboxy group, and a halogen atom (for example, a fluorine atom.) a chlorine atom, a bromine atom, and iodine atoms are mentioned -- heterocycle (for example, 0 to 1 or oxygen atom **** heterocycle is mentioned in 1 to 2, and an oxygen atom, and, specifically, a nitrogen atom) for example, pyrrolidine, pyrrolidone, piperidine, imidazole, morpholine, and franc ** is mentioned. etc. -- it is mentioned.
[0017]As the number of the substituents in the substitution carbamoyl group and substituted alkyl carbamoyl group of $R^5$, 1 or the same or different plurality is mentioned, 1 to 3 which is specifically the same or different is mentioned, and 1 to 2 [ same or different ] is preferred. As an alkyloxy carbonyl group in $R^5$, For example, it is mentioned by the alkyloxy carbonyl group of the carbon numbers 2-7, and specifically, For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As an annular carbamoyl group in $R^5$, For example, a dialkyl carbamoyl group (as a dialkyl carbamoyl group portion) For example, as a dialkyl carbamoyl group of the carbon numbers 2-12, For example, dimethylcarbamoyl, diethylcarbamoyl, ethyl methylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl, etc. mention -- having -- the basis united via combination or a hetero atom (a nitrogen atom or an oxygen atom) being mentioned, and specifically, N-pyrrolidinyl carbonyl, N-piperidinyl carbonyl, N-morpholinyl carbonyl, N-PIRARIJI nil carbonyl **********. As a substituent of the annular carbamoyl group of $R^5$, an alkanoyl group (for example, the alkanoyl group of the carbon numbers 2-6 is mentioned, and, specifically, acetyl, propanolybutanoly, heptanoly, hexanoly, etc. are mentioned.) etc. are mentioned. As an alkyloxy carbonyl group in $R^5$, For example, it is mentioned by the alkyloxy carbonyl group of the carbon numbers 2-7, and specifically, For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As a substituent in the substitution alkyloxy carbonyl group of $R^5$, Cycloalkyloxy carbonyloxy group (for example, cycloalkyloxy carbonyloxy group of the carbon numbers 4-8 is mentioned, and, specifically) for example, cyclopropyloxy carbonyloxy, cyclobutyloxy carbonyloxy, cyclopenthyloxycarbonyloxy, cyclohexyloxy carbonyloxy, etc. are mentioned. etc. -- it is mentioned.
[0018]As an alkyloxy carbonyl group in $R^6$, For example, it is mentioned by the alkyloxy carbonyl group of the carbon numbers 2-7, and specifically, For example, methyloxycarbonyl, ethyloxy carbonyl, propyloxy carbonyl, 2-propyloxy carbonyl, butyloxy carbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc. are mentioned. As a substituent in the substitution alkyloxy carbonyl group of $R^6$, Cycloalkyloxy carbonyloxy group (for example, cycloalkyloxy carbonyloxy group of the carbon numbers 4-8 is mentioned, and, specifically) for example, cyclopropyloxy carbonyloxy, cyclobutyloxy carbonyloxy, cyclopenthyloxycarbonyloxy, cyclohexyloxy carbonyloxy, etc. are mentioned. etc. -- it is mentioned.
[0019]The 2nd mode of this invention is related with the matrix-metallo-protease activity inhibition agent which makes this invention compound an active principle. this invention compound is metabolized in the living body, and shows the effective matrix-metallo-protease inhibiting activity as hydroxamic acid. And since oral absorbency is high, it is a matrix-metallo-protease activity inhibition agent useful also as a prodrug, and useful as an oral absorption agent. The matrix-metallo-protease activity inhibition agent of this invention shows remarkable inhibitory action to MMP-13 or MMP-3 especially. [0020]The 3rd mode of this invention is related with articular disease treating agents, such as modification arthrosis which makes this invention compound an active principle, and rheumatoid arthritis, cancer metastasis inhibitor or an anti-medical-treatment-for-inflammation agent, and a periodontitis treating agent. Since this invention compound shows remarkable inhibitory action to MMP-13 or MMP-3 especially, it can use it as articular disease treating agents, such as modification arthrosis and rheumatoid arthritis, or a treating agent of diseases, such as periodontosis.
[0021]The heterocyclic compound which is a medicinal active principle of this invention can be made into the salt permitted on pharmaceutical sciences. As a salt permitted on pharmaceutical sciences, acid addition salt and base addition salt are mentioned. As acid addition salt, for example Inorganic acid salts, such as a hydrochloride, hydrobromate, and sulfate, Organic acid salt, such as citrate, an oxalate, a malic acid salt, a tartrate, fumarate, and a maleate, is mentioned, and organic base salts, such as inorganic base salts, such as sodium salt and calcium salt, a meglumine salt, and a trishydroxymethylaminomethane salt, are mentioned as base addition salt. Solvates, such as a hydrate etc. of the salt permitted on a benzothiazine 3-one derivative or its pharmaceutical sciences, are also included in this invention.
[0022]The compound of formula (3) - (5) expressed with the formula (1) of this invention can be manufactured by the following methods and the method according to it.
[Chemical formula 3]



[Chemical formula 4]



The inside Z of [type expresses hydrogen or an alkaline metal atom, and $R^2$ and $R^3$ are formula:[Chemical formula 5].

($R^9$ in a formula expresses the alkyl group which may be replaced, or the amino group which may be replaced.) -- the alkyl group which may be replaced is expressed. $R^7$ and $R^8$ are formula:[Chemical formula 6].

($R^{10}$ in a formula expresses the alkyl group which may be replaced,) -- the alkyl group which may be replaced, or the amino group which may be replaced is expressed. $Y^1$ and $Y^2$ express a hydrogen atom, a hydroxyl group, a chlorine atom, a bromine atom, or iodine atoms. In the reaction of]-type 2 compound and the compound of the formula 6, $R^2$ is formula:[Chemical formula 7].

($R^{10}$ is synonymous with the above among a formula.) -- $R^7$ [ in / when expressed / the formula 6 ] -- formula:[Chemical formula 8]

($R^{10}$ is synonymous with the above among a formula.) -- $Y^1$ can carry out to peptide chemistry in accordance with publicly known methods (the foundation of peptide synthesis, "experiment" spring store Nobuo et al., Maruzen, etc.) using the compound which is a hydroxyl group, a chlorine atom, a bromine atom, or iodine atoms. for example, the C end activating method (an acid halide method, an acid azide method, and a mixed acid anhydride method.) A method (how to use DCC (N,N'-dicyclohexylcarbodiimide) etc.), the N end activating methods, etc. for using coupling reagents, such as an active ester method and a symmetrical acid anhydride (the isocyanate method, the HOSUFAZO method, the phosphorous acid ester process, etc.) are mentioned. As a method of using a coupling reagent, for example the compound of the formula 2, and the compound of the formula 6, It is an N-(dimethylaminoethyl)-N'-ethylcarbodiimide in N.N-dimethylformamide (DMF). The method of condensing, etc. are mentioned at 0 ** - a room temperature under a hydrochloride (WSC hydrochloride) and 1-hydroxybenzotriazol (HOBt) existence. The alkyl group by which $R^7$ in the formula 6 may be replaced when it is the alkyl group by which $R^2$ may be replaced, Although it can obtain by making it react at a room temperature the bottom of the nucleophilic substitution for which $Y^1$ is usually used using the compound which is a chlorine atom, a bromine atom, or iodine atoms, for example, potassium carbonate, and base existence like DBU, and among DMF, An alkaline metal like sodium is preferred for Z of the compound of the formula 2. $R^2$ -- formula: -- [Chemical formula 9]

$R^9$ in [type expresses the amino group which may be replaced. The amino group by which $R^7$ in the formula 6 may be replaced in], It can obtain by making it react at a room temperature the bottom of coexistence of the urethane formation reaction for which $Y^1$ is usually used using the compound which is a hydrogen atom, for example, carbonyldiimidazole, phosgene, etc., and among THF. Formula 8 [0023]

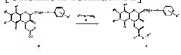
[Chemical formula 10]

$R^1$ in [type - $R^2$, $R^4$-$R^6$, X, and n are synonymous with the above. The compound expressed with] is also compoundable by a single step to the compound of the formula 2 by the above-mentioned method using the compound of an excessive amount of formulas 6, and other reaction reagents. It is formula [Chemical formula 11] to the compound of the formula 2.

Q expresses among [type the alkylene which may be replaced and Y1 and Y2 are synonymous with the above.

A compound including heterocycle is compoundable by using the compound expressed with] on the above and the conditions. The compound of the formula 3 can also be manufactured by a lower type.

[Chemical formula 12]



$R^1$ in [type - $R^2$, $R^4$-$R^6$, X, and n are synonymous with the above. ] $R^2$ among the reactions of the compound of the formula 2 of the above [ this reaction ] and the compound of the formula 6 is formula:[Chemical formula 13].

($R^{10}$ is synonymous with the above among a formula.) -- when expressed, it can be based on the same method as what was used. The compound expressed with the formula 4 can be obtained from the compound of the formula 3, and the compound of the formula 7 by the method which obtained the compound of the formula 3 from the compound of the formula 2, and the same method. the protective group of the hydroxyl group by which the compound of the formula 5 is expressed with $R^2$ of the compound of the formula 4 -- a law -- it can obtain by carrying out deprotection in accordance with a method. For example, deprotection can be carried out by processing with hydrocracking, hydrolysis, or the Lewis acid in a nonaqueous solution. Using hydrogenation catalysts (for example, palladium catalyst etc.) for example as a reaction of hydrocracking, among an inertness organic solvent (for example, methanol, ethanol, etc.), if needed, acid, such as acetic acid and chloride, can be added and it can react at a room temperature under a hydrogen atmosphere. As a reaction of hydrolysis, for example Acetic acid, trifluoroacetic acid, methanesulfonic acid, Sulphur-containing compounds, such as an anisole or thioanisole, a dimethylsulfide, and ethanedithiol, can be added among a non-solvent or a hydrous organic solvent if needed under acid existence, such as p-toluenesulfonic acid, sulfuric acid, chloride, and hydrobromic acid, and it can react at a room temperature. Or it can also be based on the boron tribromide in the inside of aprotic solvents, such as a methylene chloride, boron trichloride, and iodination trimethylsilane. However, as for the protective group expressed with $R^2$, it is preferred to choose the protective group of a hydroxyl group expressed with $R^3$ and the protective group from which deprotection conditions differ.

[0024]The intermediate field for manufacturing the compound or it which is contained in this invention expressed with a formula (1) can be refined by the usual method. For example, it can refine by column chromatography, recrystallization, etc. As a recrystallization solvent, for example Alcoholic solvent, such as methanol, ethanol, and 2-propanol, These mixed solvents [, such as a hydrocarbon system solvent, ], such as ketone solvent, such as aromatic hydrocarbon system solvents, such as ester solvent, such as ether system solvents, such as diethylether, and ethyl acetate, and toluene, and acetone, and hexane, are mentioned. If necessary when performing an above-mentioned reaction, the technology of protection and deprotection can be used. About the technology of protection and deprotection. It is describing in detail at (T. W. Greene and P. G. M. Wuts, "Protecting Groups in Organic Synthesis", 1991, JOHN WILEY & SONS, INC.). The benzothiazine 3-one derivative of this invention or its salt may form solvates, such as a hydrate, and this invention also contains these.

[0025]If the benzothiazine 3-one derivative of this invention or its salt may have a substituent which has asymmetrical carbon and is in such a compound when dissymmetry arises or, an optical isomer exists. The mixture and the thing which isolated of each of these isomers are included in this invention compound. As a method of obtaining such an optical isomer purely, optical resolution is mentioned, for example. as an optical-resolution method -- a benzothiazine 3-one derivative or its intermediate field -- the inside of an inert solvent (for example, methanol.) Ether system solvents, such as alcoholic solvent, such as ethanol and 2-propanol, and diethylether, Aromatic hydrocarbon system solvents, such as ester solvent, such as ethyl acetate, and toluene, These mixed solvents, optical activity acid, such as acetonitrile. for example, monocarboxylic acid, such as mandelic acid, an N-benzyloxy alanine, and lactic acid,. Sulfonic acid and salts, such as dicarboxylic acid, such as tartaric acid, o-diisopropylidenetartaric acid, and malic acid, camphor sulfonic acid, and bromo camphor sulfonic acid, can also be made to form. When a benzothiazine 3-one derivative or its intermediate field have acidic substituents, such as a carboxyl group, optical activity amine (for example, organic amine, such as alpha-phenethylamine, kinin, quinidine, cinchonidine, cinchonine, and strychnine) and salt can also be made to form.

[0026]As a temperature in which a salt is made to form, the range of the boiling point of a solvent is mentioned from a room temperature. In order to raise optical purity, it is desirable to once raise temperature to near the boiling point of a solvent. Before separating the salt which deposited, it can cool if needed, and yield can be raised. the amount of optical activity acid used or amine receives a substrate -- about 0.5- the range of about 2.0

Eq -- the range of around 1 Eq is preferably suitable. accepting necessity -- a crystal -- the inside of an inert solvent (for example, alcoholic solvent, such as methanol, ethanol, and 2-propanol,.) It recrystallizes with these mixed solvents, such as aromatic hydrocarbon system solvents, such as ester solvent, such as ether system solvents, such as diethylether, and ethyl acetate, and toluene, and acetonitrile, and an optical activity high grade salt can also be obtained. The obtained salt can be processed with acid or a base by the usual method if needed, and a free object can also be acquired.

[0027]An oral target or a parenteral target can be medicated with the benzothiazine 3-one derivative of this invention, or its salt. When prescribing a medicine for the patient in taking orally, a medicine can be prescribed for the patient by the dosage form usually used. Parenterally, a medicine can be prescribed for the patient in forms, such as a local administration agent, injections, an endermic agent, and a pernasal agent. As an oral agent or a rectum administration agent, a capsule, a tablet, a pill, powder medicine, cachets, a suppository, liquids and solutions, etc. are mentioned, for example. As injections, a sterile solution or suspension etc. is mentioned, for example. As a local administration agent, cream, ointment, a lotion, an endermic agent (the usual patch agent, a matrix agent), etc. are mentioned, for example. The above-mentioned dosage forms are the usual methods, and are manufactured with the excipient and additive agent which are permitted pharmacologically. As the excipient permitted pharmacologically and an additive agent, a carrier, a binding material, perfume, a buffer, a thickening agent, colorant, stabilizer, an emulsifier, a dispersing agent, a suspending agent, an antiseptic, etc. are mentioned. As a carrier permitted pharmacologically, for example Magnesium carbonate, magnesium stearate, Talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting point wax, cacao butter, etc. are mentioned. A capsule can be manufactured by putting this invention compound into inside with the carrier permitted pharmacologically. It can mix with the excipient permitted pharmacologically, or the benzothiazine 3-one derivative of this invention or its salt can be put without an excipient in a capsule. Cachets can also be manufactured in a similar way.

[0028]A solution, suspension, an emulsion, etc. are mentioned as liquids and solutions for injection. For example, solution, a water-propylene glycol solution, etc. are mentioned. Liquids and solutions can also be manufactured in the form of the solution of the polyethylene glycol or/and propylene glycol which may also contain water. The suitable liquids and solutions for internal use can add this invention compound to water, and can manufacture colorant, perfume, a stabilizing agent, a sweetening agent, a resolvent, a thickening agent, etc. [ necessity ]. The suitable liquids and solutions for internal use add the benzothiazine 3-one derivative of this invention, or its salt to water with a dispersing agent, and can manufacture it also by using ****. The nature pharmacologically permitted as a thickening agent, for example or synthetic gum, resin, methyl cellulose, sodium carboxymethyl cellulose, or a publicly known suspending agent is mentioned.

[0029]As a local administration agent, the above-mentioned liquids and solutions and cream, aerosol, a spray, powder material, a lotion, ointment, etc. are mentioned. The above-mentioned local administration agent is mixed with the diluent and carrier which are used for the benzothiazine 3-one derivative of this invention, or [ its / salt and usual ] and which are permitted pharmacologically, and can be manufactured. Ointment and cream add a thickening agent and/or a gelling agent to a water or oily base, pharmaceutical-preparation-ize, and are obtained, for example. As this base, water, liquid paraffin, vegetable oil (peanut oil, castor oil, etc.), etc. are mentioned, for example. As a thickening agent, soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, a polyethylene glycol, lanolin, hydrogenation lanolin, beeswax, etc. are mentioned, for example. The lotion can season a water or oily base with one kind or the stabilizer beyond it permitted pharmacologically, a suspending agent, an emulsifier, a dispersing agent, a thickening agent, colorant, perfume, etc.

[0030]Powder medicine is pharmaceutical-preparation-ized with the base of the powder medicine permitted pharmacologically. Talc, lactose, starch, etc. are mentioned as a base. Drops can carry out [ **** ]-izing with a water or non-aqueous base, a kind or the dispersing agent beyond it permitted pharmacologically, a suspending agent, a resolvent, etc. A local administration agent may also contain antiseptics, such as hydroxymethyl benzoate, hydroxybenzoic acid propyl, chlorocresol, and benzalkoniumchloride, and a bacterial-growth inhibitor if needed. The pharmaceutical preparation which made the benzothiazine 3-one derivative of this invention or its salt the liquids-and-solutions spray, the powder medicine, or drops made into an active principle can be prescribed for the patient in pernasality. usually receiving an adult, in administering orally although a dose and frequency of administration change with condition, age, weight, dosage forms, etc. -- per day -- about 1- the range of about 500 mg -- desirable -- about 5- the range of about 100 mg can be prescribed for the patient in 1 time or several steps. the case where a medicine is prescribed for the patient as injections -- about 0.1- the range of about 300 mg -- desirable -- about 1- the range of about 100 mg can be prescribed for the patient in 1 time or several steps.

[0031]
[Working example]Although an working example explains this invention concretely below, this invention is not limited at all by these working examples.
Working-example 14-(2-{(ethoxycarbonyl) [(ethoxycarbonyl) oxy] amino}-2-oxo ethyl)-3-oxy-2-[4-(trifluoromethoxy) benzyl]-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid. [Chemical formula 14]

4-. (2-{.) (Ethoxycarbonyl) [(ethoxycarbonyl) oxy] amino}-2-oxoethyl-3-oxy-2-[4-(trifluoromethoxy) benzyl]-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid t-butylester (520 mg) The 5%-ethanedithiol content TFA (2 ml) was added to 0.79mmol, and it settled at the room temperature for 3 hours. By adding and carrying out vacuum concentration of the toluene, and refining residue with silica gel column chromatography (chloroform: acetic acid =100:1), 375 mg of 4-(2-{(ethoxycarbonyl) [(ethoxycarbonyl) oxy] amino}-2-oxo ethyl)-3-oxy-2-[4-(trifluoromethoxy) benzyl]-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid was obtained. 1 H-NMR(DMSO-$d_6$, deltappm): 1.22-1.36 (6H, m), 2.80 (1H, m), 3.14 (1H, m), 4.09 (1H, br-s), 4.31-4.43 (4H, m), 4.62 (0.1H, d, J= 20 Hz), 4.76 (0.1H, d, J= 20 Hz) 5.00-5.49 (1.8H, m), 7.26(2H, br-s),7.35(2H, br-d, J=8.0Hz),7.51-7.59(2H, m), 7.64(1H, dd, J=1.2Hz, 9.2Hz)13.2(1H, br-s)
[0032]Working-example 24-. (2-{(ethoxycarbonyl) [(ethoxycarbonyl) Oxy] Amino}-2-oxo ethyl) By a method similar to the method of a description in the-2-(4-fluorobenzyl)-3-oxy-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid working example 1.4-(2-{(ethoxycarbonyl) [(ethoxycarbonyl) oxy] amino}-2-oxo ethyl)-2-(4-fluorobenzyl)-3-oxy-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid was obtained.
[Chemical formula 15]

1H-NMR(DMSO-$d_6$, deltappm): 1.27 (6H, m), 2.75 (1H, m), 3.14 (1H, br-s), 4.02 (1H, br-s), 4.34-4.42 (4H, m), 5.11-5.49 (2H, m), 7.09(2H, br-s), 7.23(2H, br-s), 7.53(1H, d, J=8.0Hz), 7.57(1H, br-s), 7.64(1H, dd, J=1.4Hz, 8.0Hz),13.2(1H, br-s)
[0033]Working-example 34-[2-. ([.) (Benzyl) Carbonyl] {[(benzyl) carbonyl] oxy} amino-2-oxo ethyl] by a method similar to the-3-oxy-2--3,4-[ [4-(trifluoromethoxy) benzyl] ] dihydro-2H-1,4-benzothiazine 6-carboxylic acid working example 1.4-[2-{[(benzyl) carbonyl {[(benzyl) carbonyl] oxy}] amino)-2-oxo ethyl]-3-oxy-2-[4-(trifluoromethoxy) benzyl]-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid was obtained.
[Chemical formula 16]

1H-NMR(DMSO-$d_6$, deltappm): 2.84 (1H, br-s), 3.19 (1H, br-s), 4.07 (1H, br-s), 5.33-5.51(4H, m), 7.24(2H, br-s), 7.31-7.40(12H, m), 7.53(1H, d, J=8.0Hz),7.59(1H, br-s), 7.63(1H, d, J=8.0Hz)
[0034]Working-example 42-. (4-chlorobenzyl) By a method similar to the-4-(2-{(i-carbopropoxy) [(i-carbopropoxy) oxy] amino}-2-oxo ethyl)-3-oxy-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid working example 1.2-(4-chlorobenzyl)-4-(2-{(i-carbopropoxy) [(i-carbopropoxy) oxy] amino}-2-oxo ethyl)-3-oxy-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid was obtained.
[0035]
[Chemical formula 17]

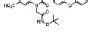
1 H-NMR(DMSO-$d_6$, deltappm): 1.27-1.38 (12H, m), 2.75 (1H, dd, J= 9.4 Hz, 14.0 Hz), 3.14 (1H, m), 4.05 (1H, m), 4.95 (1H, m), 5.10 (1H, m), 5.05-5.50 (2H, m), 7.23 (2H, d, J= 8 Hz), 7.32 (2H, bs), 7.51 (2H, m), 7.63 (1H, d, J= 8.4 Hz), 13.19 (1H, bs).
[0036]Working example 5-3,4-Dihydro-2H-1,4-benzothiazine 6-carboxylic acid 4-{2-[(benzyl) amino]-2-oxo ethyl}-2-(4-chlorobenzyl)-3-oxy [0037]
[Chemical formula 18]

[6-(t-butoxycarbonyl)-2-(4-chlorobenzyl)-3-oxy-2,3-dihydro-4H-1,4-benzothiazine 4-yl] Acetic acid (500 mg)

is melted in THF (3 ml), N-methyl morpholine (130microl) and chloroformic acid isobutyl (152microl) were added at 0 **, and it stirred for 5 minutes. Subsequently, DMF (3 ml), O-benzylhydroxylamine hydrochloride (215 mg), and N-methyl morpholine (148microl) were added, and it stirred at the room temperature for 30 minutes at 0 ** for 15 hours. After adding 1N HCl (3 ml) and stirring for 15 minutes, the reaction mixture was diluted with water. After ethyl acetate extracted this, the saturated sodium chloride solution washed the organic layer. The organic layer was dried with anhydrous magnesium sulfate, the ** exception carried out the drier and vacuum concentration was carried out. The silica gel column (hexane: silica gel: 50 g, solvent : ethyl acetate =4:1, subsequently 3:1) refined the residue, and the oily matter was obtained. This is melted in a methylene chloride (5 ml), and they are the bottom of 0 **, an anisole (2 ml), and TFA (5 ml). In addition, it stirred at the room temperature at 4:00. After repeating twice the operation which adds toluene to a reaction mixture and carries out vacuum concentration, The obtained colorless crystal was ****(ed) by ether hexane, and 4-{2-[(benzyl) amino]-2-oxo ethyl}-2-(4-chlorobenzyl)-3-oxy-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid (380 mg) was obtained. 1H-NMR(DMSO-$d_6$, deltappm): 2.76 (1H, dd, J= 8.8, 13.9 Hz), 3.15 (1H, dd, J= 6.4, 14.0 Hz), 4.01 (1H, m), 4.40-5.10 (4H, m), 7.23-7.47 (9H, m), 7.51(1H, d, J=8.0Hz), 7.62(1H, d, J=8.0Hz), 7.68(1H,s), 11.11 and 11.53(1H, each s), 13.21(1H, br-s).

[0038]working-example 64- [2-(t-butoxyamino)-2-oxo ethyl]-2-by a method similar to the [4-(4-methoxy phenoxy) benzyl]-3-oxy-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid working example 5.4-[2-(T-butoxyamino)-2-oxo ethyl]-2-[4-(4-methoxy phenoxy) benzyl]-3-oxy-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid was obtained.

[Chemical formula 19]



1 H-NMR(DMSO-$d_6$, deltappm): 1.16 and 1.27 (9H, each s), 2.72 (1H, m), 3.09 (1H, m), 3.74 (3H, s), 3.93 (1H, m), 4.51 (1H,d,J=16Hz), 4.62 (1H,d,J=16Hz), 6.78 (2H,d,J=8Hz), 6.96 (4H, m), 7.17 (2H,d,J=8Hz), 7.49(1H,d,J=8Hz),7.60(1H,dd,J=1.6,8Hz),7.64(1H,s),10.54 and 10.80(1H,each s),13.13(1H,br-s)

[0039]By a method similar to the working-example 72-(4-chlorobenzyl)-3-oxy-4- {2-oxy-2-[(tetrahydro 2H-pyrane-2-yloxy) amino] ethyl}-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid working example 5.2-(4-chlorobenzyl)-3-oxy-4- {2-oxy-2-[(tetrahydro 2H-pyrane-2-yloxy) amino] ethyl}-3,4-dihydro-2H-1,4-benzothiazine 6-carboxylic acid was obtained.

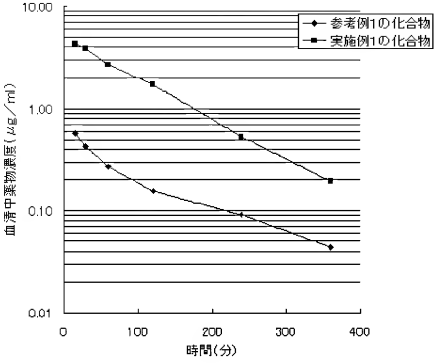
[Chemical formula 20]



1 H-NMR(DMSO-$d_6$, deltappm): 1.53-1.67 (6H, m), 2.74 (1H, m), 3.13 (1H, m), 3.54 (1H, m), 3.93(2H, m), 4.42-4.86(3H, m),7.25(2H, m), 7.32(2H, m), 7.41(1H,d, J=7.89Hz), 7.61-7.66(2H, m), 11.51(1H, br-s)

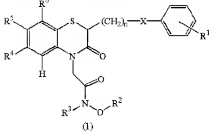
## DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
The evaluation test of the oral absorbency using the rat in the example 1 of an examination




## CLAIMS

[Claim(s)]
[Claim 1]A formula (1)
[Chemical formula 1]



(1)

(X express a single bond, a sulfur atom, or an oxygen atom among a formula, and n) Express an integer of 1-6 and $R^1$ A hydrogen atom, a halogen atom, An alkyl group which may be replaced, an alkoxy group which may be replaced, an alkyl sulfonyl group, Express an aryloxy group or a heteroaryloxy group which may be replaced which may be replaced, and $R^2$, A hydrogen atom, alkyloxy carbonyl which may be replaced, alkyl which may be replaced, Express a carbamoyl group which may be replaced, or an annular carbamoyl group which may be replaced, or $R^3$, Or [ it expresses a hydrogen atom, alkyloxy carbonyl which may be replaced, or alkyl which may be replaced (however, $R^2$ and $R^3$) ], it does not become a hydrogen atom simultaneously. Or $R^2$ and $R^3$ join together, express heterocycle and $R^4$, A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl group, a substituted alkyl group, Express an alkyl sulfonyl group, a carbamoyl group which may be replaced, or an alkyloxy carbonyl group which may be replaced, and $R^5$ A hydrogen atom, a carboxy group, a tetrazolyl group, an imidazolyl group, a substituted alkyl group, Express an alkyl sulfonyl group, a carbamoyl group which may be replaced, an annular carbamoyl group which may be replaced, or an alkyloxy carbonyl group which may be replaced, and $R^6$, A hydrogen atom, a carboxy group, or an alkyloxy carbonyl group that may be replaced is expressed. A benzothiazine 3-one derivative expressed or its salt.

[Claim 2]The benzothiazine 3-one derivative according to claim 1 whose n is an integer of 1 to 4, or its salt.
[Claim 3]The benzothiazine 3-one derivative according to claim 1 or 2 whose $R^1$ is a halogen atom, an alkoxy group which may be replaced, an alkyl sulfonyl group, an aryloxy group which may be replaced, or a heteroaryloxy group which may be replaced, or its salt.
[Claim 4]The benzothiazine 3-one derivative according to claim 3 whose X is a single bond, or its salt.
[Claim 5]The benzothiazine 3-one derivative according to claim 4 whose n is 1, or its salt.
[Claim 6]$R^4$ A carboxy group, a tetrazole group, an imidazole group, a substituted alkyl group, The benzothiazine 3-one derivative according to any one of claims 1 to 5 which is an alkyl sulfonyl group, a carbamoyl group which may be replaced, or an alkyloxy carbonyl group which may be replaced, or its salt.
[Claim 7]$R^5$ A carboxy group, a tetrazole group, an imidazole group, a substituted alkyl group, The benzothiazine 3-one derivative according to any one of claims 1 to 5 which is an alkyl sulfonyl group, a carbamoyl group which may be replaced, an annular carbamoyl group which may be replaced, or an alkyloxy carbonyl group which may be replaced, or its salt.
[Claim 8]The benzothiazine 3-one derivative according to any one of claims 1 to 7 whose $R^1$ is a trifluoro methoxy group, or its salt.
[Claim 9]The benzothiazine 3-one derivative according to any one of claims 1 to 7 which is an aryloxy group by which $R^1$ may be replaced, or its salt.
[Claim 10]A medicinal composition containing a benzothiazine 3-one derivative according to any one of claims 1 to 9 or its salt.
[Claim 11]Matrix-metallo-protease inhibitor which makes an active principle a benzothiazine 3-one derivative according to any one of claims 1 to 9 or its salt.
[Claim 12]An articular disease treating agent which makes an active principle a benzothiazine 3-one derivative according to any one of claims 1 to 9 or its salt.
[Claim 13]Cancer metastasis inhibitor which makes an active principle a benzothiazine 3-one derivative according to any one of claims 1 to 9 or its salt.
[Claim 14]An anti-medical-treatment-for-inflammation agent which makes an active principle a benzothiazine 3-one derivative according to any one of claims 1 to 9 or its salt.
[Claim 15]A periodontitis treating agent which makes an active principle a benzothiazine 3-one derivative according to any one of claims 1 to 9 or its salt.